REMARKS

Claims 35-41 and 69-74 are in the case. Claims 1-34 and 42-68 are canceled.

Claims 69, 70 , 71 and 72 are new claims. Basis is found in claims 36 and 39 and 41 and in the application as filed. For ease of reference, reference to the application as filed will be made to the corresponding U.S. Patent Publication No. US 2005/0131063. For basis see [0043], [0056], [0057], [0069], [0070] and Figure 1 of US 2005/0131063.

Claims 73 and 74 are new claims. Basis for claims 73-74 is found in claim 37 as filed taken with admissions in the Office Action that there is enablement for dihydrolipoic acid for treating angina.

Basis for the amendment to claim 35 together with a discussion of the invention is presented below.

The invention involves the discovery that mtALDH is the enzyme responsible for catalyzing the bioactivation of nitroglycerin in the human vasculature and that its inactivation underlies the occurrence of nitroglycerin tolerance [0166], and that oxidation by nitroglycerin causes mtALDH inactivation [0169] and that dithiols and certain reductants activate mtALDH which has been inactivated [0169] and [0170]. Obviously tolerance occurs when insufficient active mtALDH is present to bioactivate nitroglycerin (cause formation of 1,2-glyceryl dinitrate and nitrite [0155]). Obviously tolerance is reversed or postponed when inactivated mtALDH is caused to be activated. The invention further involves the discovery that dithiols and certain reductants activate

inactivated mtALDH ([0011] and [0038]).

We turn now to the rejection and firstly to the prior art rejections.

Claims 35-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Weischer et al. DE 4420 102 A (a machine translation into English is supplied). Reconsideration is requested.

Please note that the claims are now limited to reversing and postponing the occurrence of nitroglycerin tolerance.

As indicated in the result section of Weischer (fourth paragraph on page 2), nitroglycerin plus alpha-lipoic acid gives stronger effect than nitroglycerin alone. Weischer describes a synergistic effect (12th paragraph of page 2 of the results translation). In other words, Weischer's treatment is a substitute for increased dosage of nitroglycerin. While Weischer may inherently embrace prevention of nitroglycerin tolerance from occurring, it does not suggest that nitroglycerin tolerance can be reversed or postponed. Note that Weischer doesn't teach administration of alpha-lipoic acid after nitroglycerin has been administered so reversal and postponement are not inherent in its disclosure. Note that the claims are now limited to reversal and postponement. Thus Weischer doesn't anticipate.

Claims 35-38 and 40 are rejected as being obvious over Murphy, Br. Journal of Pharmacology 128, 435-443 (1998) taken with Laursen et al., Circulation 94, 2241-2247 (1996). Reconsideration is requested.

Murphy is defective to teach reversal or postponement of nitroglycerin tolerance.

In no case is nitroglycerin administered alone before DTT is administered. In Murphy, note pages 435-439, which indicate that DTT is a preservative for nitroglycerin caused relaxation when it is initially administered together with the nitroglycerin, i.e. it prevents the occurrence of nitroglycerin tolerance. It does not suggest that DTT will reverse or postpone the occurrence of nitroglycerin tolerance that will occur when nitroglycerin is administered initially without DTT. Laursen seems to be cited to show that reduced biological activity of nitric oxide contributes to in vivo development of nitrate tolerance. This is wrong since the instant application (Background Example 1) shows that nitroglycerin tolerance is due to attenuated biotransformation of nitroglycerin catalyzed by mtALDH, because nitroglycerin oxidizes mtALDH. Laursen is submitted to be irrelevant.

Claim 39 is rejected as obvious over Murphy in view of Laursen et al. further in view of Pruijn et al. Felt Wissenshaft Technologies/Fax Science Technology 93(6), 216-221 (2006). Reconsideration is requested.

The rejection is defective for the same reasons as the rejection of claims 35-38 and 40 based on Murphy and Laursen et al. discussed above.

Claim 41 is rejected as obvious over Murphy in view of Getz, E.B., et al. Analytical Biochemistry 273, 73-80 (1999). Reconsideration is requested.

The rejection is defective for the same reasons as claims 35-39 and 40 based on Murphy and Laursen et al. discussed above.

We turn now to the patentability of claims 73-74 over Weischer et al. and Murphy

plus Laursen et al. plus Pruijn. It is noted that the dosage for the synergism of Weischer is less than the dosage in the instant invention for treating angina. (2 – 40 mg at page 4 of the machine translation versus 50 mg/k in Example XXXII of the instant application) The combination of Murphy plus Laursen plus Pruijn is also defective vis-à-vis claims 73-74 because Murphy doesn't indicate reductant generally preserves nitroglycerin relaxation of arteries but only DTT, and doesn't enable treatment of angina if the same standards for enablement are applied to Murphy as are applied in the Office Action.

We turn now to the rejections under 35 U.S.C. 112.

Claims 35-41 are rejected under 35 U.S.C. 112, first paragraph, on the basis that the applicants did not have in mind at the time of filing all the diseases associated with those in need of nitroglycerin therapy. It is noted that this objection does not apply to claims 36-41 and 69-70. Furthermore, the rejection is based on the assertion that one skilled in the art would not know or could not determine all those in need of nitroglycerin therapy. The case law is that the burden is on the PTO to show this; this is not done. Moreover, the position is a "red herring". Those prescribed nitroglycerin are obviously the group involved.

A position is also taken that applicant was not in possession of all mitochondrial selective dithiols and reductants capable of activating mtALDH or apparently that one could not even determine what a mitochondrial selective thiol is. Firstly, the rejection does not apply to claims 39, 41, 69-72. Secondly, the burden is on the PTO to show

that one skilled in the art could not determine what a mitochondrial selective thiol is. The ipse dixit that "the description is inadequate for one skill(ed) in the art to distinguish what the inventors were in possession of," is inadequate to meet this burden.

Note further that no case law is cited to support this type of lack of description rejection. This type of rejection is traditionally asserted when the words of a claim are different from and broader than words in the application as originally filed. This is not the case here. The words complained about are the same as words in the application as filed. In regard to this consider the following from In re Robbins, 166 U.S.P.Q. 552,555 (CCPA, 1970).

> If the examiner and/or the board intended a rejection under the first paragraph of Sec. 112, it must be reversed inasmuch as the specification contains a statement of appellant's invention which is as broad as appellant's broadest claims, and inasmuch as the sufficiency of the specification to satisfy the 'best mode' requirement of Sec. 112 and to enable one skilled in the art to practice appellant's process as broadly as it is claimed has not been questioned.

Here enablement is questioned and the issue is treated below.

Claims 35-41 are rejected under 35 U.S.C. 112, first paragraph, on the basis that the specification does not provide enablement for every coronary syndrome and condition, restenosis, asthma or rectal spasm. Reconsideration is requested.

The undersigned does not understand and cannot make sense of the word "every". There is no requirement for a specific example for everything within the scope of a broad claim. In re Anderson, 176 U.S.P.Q. 331,333 (CCPA, 1973).

See also In re Goffe, 191 U.S.P.Q. 429,431 (CCPA, 1976) wherein the court stated:

> For all practical purposes, the board would limit appellant to claims involving the specific materials disclosed in the examples, so that a competitor seeking to avoid infringing the claims would merely have to follow the disclosure in the subsequently-issued patent to find a substitute. However, to provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

Consider further that "Any assertion by the Patent Office that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasons substantiating the doubts so expressed." In re Dinh-Nguyen and Stenhagen, 181 U.S.P.Q. 46,47 (CCPA, 1974). See also In re Bowen, 181 U.S.P.Q. 48 (CCPA, 1974); In re Gardner, 177 U.S.P.Q. 396,397 (CCPA, 1973). Such evidence and reasons are not present in the rejection.

Routine application of the Wards factors does not substitute for the required evidence. See especially Ex parte Reese, 40 U.S.P.Q.2d 1221 (Pat. Off. Bd. of Pat. App. and Int. 1996).

It is noted that any response that does not cite countering case law will be considered by the undersigned to be frivolous.

The enablement rejection is also applied to the treating agents except for DTT,

DHLA and tris(2-carboxyethylphosphine) vis-à-vis angina. As indicated above, applicant doesn't have to prove anything. The burden is on the PTO to present evidence this has not been done.

Objection is made to the term "prevent" or "reverse" as absolute definitions. The term "prevent" is no longer in the claims. The Office Action position in respect to "reverse" demonstrates a misunderstanding of what happens in the invention. All that has to happen is that mtALDH that is inactivated so that it cannot catalyze conversion of nitroglycerin is activated so that it can catalyze conversion. In real life the scenario is, nitroglycerin doesn't work. Treating agent is then administered so that mtALDH can catalyze conversion of nitroglycerin and nitroglycerin then does work. Reversal has occurred.

An editorial comment follows: It is stylish for the PTO to render lack of written description and lack of enablement rejections where specific diseases and treating compounds are not claimed. But the case law is against this and the reason is so that inventions can be commercialized. Who is going to sink $100,000,000 into FDA clearance when another party can avoid the claims by brainstorming alternatives to the specifics that are claimed. So what happens? FDA clearance is not initiated, and patients die. It seems to the undersigned that the routine use of 112 rejections in cases that are always reversed on appeal means when the PTO knows or should know that life saving treatments will be delayed, is inappropriate. It is noted that the undersigned has been appealing these types of 112 rejections for at least fifteen years and has

never lost on appeal.

Allowance is requested.

Respectfully submitted,
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